

35 USC §103

The examiner has rejected claims 1-7, 27 and 28 as obvious over Laboureur in view of Reedy and Riggs or Neilsen, in further view of Janson, Mannson-Rahemtulla, Nakagawa or Berton. This rejection or one similar has been advanced in each of the three Office Actions issued in connection with this case and its parent, U.S. Serial No. 07/659,408. Twice, applicants have provided what they consider to be sound reasoning and solid evidence for the patentability of the rejected claims over the cited references. The examiner, however, remains unpersuaded.

To the extent that applicants may not yet have fully illuminated their position, a brief recap of the rejection, and the perceived defects therein, will be provided. In addition, the last Office Action raised several new legal and factual points which applicants seek to address here.

A. The Rejection

The primary references are Laboureur and Reedy. Laboureur is said to teach isolation of urate oxidase (UO) from *A. flavus*. Reedy is said to teach the isolation of UO from rat cells. Riggs and Nielsen are said to teach methods of recombinant protein production. Janson, Mannson-Rahemtulla, Nakagawa and Berton all are said to teach methods of affinity purification.

According to the examiner, it would have been obvious to isolate the gene for Laboureur's *A. flavus* UO according to Reedy, and facilitate recombinant expression thereof according to Neilsen or Riggs. The affinity purification methods of Janson, Mannson-Rahemtulla, Nakagawa and Berton are seen as obvious, additional steps by which the claimed, high activity UO can be produced. According to the examiner, the only motivation needed to combine and/or modify any of the references stems from

the knowledge "that *A. flavus* urate oxidase performs a useful enzymatic reaction." Moreover, any failure in applying standard affinity purification methods to the claimed compositions allegedly would have been overcome simply by "vary[ing] the pH, salt concentrations, and buffers in routine experimental design to attempt to purify the enzyme."

B. Lack of a Prima Facie Case

Despite the examiner's characterization of the present invention as a trivial exercise of (i) combining prior art technologies and (ii) routinely modifying these techniques to produce the claimed product, the UO recited in the rejected claims was not reasonably suggested by any of the cited references. In their previous response, applicants offered several observations that undermined the very basis for the rejection.

First, applicants pointed out that the examiner's scenario of isolating the *A. flavus* UO gene according to Reedy would not succeed. As stated, "the RNA extraction techniques used by Reedy, while suitably applied to rat liver cells, will not work with mycelium recovered from culture of *A. flavus*." Second, it was observed that without the gene for UO, the cited art could, at best, be read as enabling the production of UO of about 8 U/mg, i.e., the UO of Laboureur. Third, applicants noted that the pseudo-affinity purification methods employed were not conventional. Rather, successful implementation of this relatively new technology occurred only after months of empirical experimentation. And fourth, the pseudo-affinity purification step was not simply "tacked on" to the end of otherwise routine, recombinant production of UO. Instead, it was an absolute requisite to obtaining sequenceable grade UO, thereby opening the door to cloning of the *A. flavus* UO gene.

Last, applicants pointed out that the examiner's analysis appeared to ignore whether those of skill in the art would have held *a priori* "likelihood of success" in arriving at the claimed invention. In other words, the examiner's rejection sounded in terms of suggested "attempts," without establishing the requisite "reasonable predictability" for the corresponding result. This sort of analysis, referred to in the case law as "obvious to try," is impermissible, and applicants urged the examiner to reconsider the rejection in light of their comments.

C. The Examiner's Rebuttal

Despite applicants' efforts, the examiner remains unpersuaded with respect to the nonobviousness of the claimed invention. Several reasons were provided by the examiner to justify maintenance of the rejection. First, the examiner believes that applicants' declaratory submission is light on "facts" and data and, therefore, cannot be afforded any serious consideration. Second, the examiner refutes applicants' contention that one could not sequence the UO prepared by Laboureur because of insufficient purity. Third, the examiner objects to applicants' suggestion that a hiatus of seventeen years between Laboureur's patent and the advance represented by the instant application was evidence of nonobvious. Fourth, the examiner states that "[i]t is not clear why the method of Reedy et al. would not work with *A. flavus*." Fifth, the examiner rankles at the notion that the rejection was based on an "obvious to try" standard. And sixth, the examiner objects to applicants' examination of the relevant methodologies when the rejected claims recite compositions.

As is readily discerned, each of the examiner's points is an attempt to undercut applicants' rebuttal position. With due respect, applicants submit that each and every one of these points is based on factual or legal misapprehensions. The

remainder of this response will provide reasons why the examiner's arguments do not, in fact, undercut applicants' position with respect to nonobviousness. In the end, applicants reasoning will put the burden of establishing obviousness back on the examiner - a burden which the examiner cannot meet.

D. The Larbre Declaration

The examiner has stated that applicants' reliance on the Larbre declaration is misplaced. According to the examiner, "[t]he Declaration is unworthy of the weight desired as it is devoid of data and light on specific facts." The kind of "data" and "facts" needed, however, are not described. Therefore, applicants are at a loss to address the examiner's concerns. Applicants request that the examiner clarify the nature of the "data" and "facts" needed to remedy the perceived deficiencies in the declaration.

Even at face value, the examiner's derision of the declaration for lack of "fact" is not well taken. In paragraph 4 of Dr. Larbre's declaration, the methods of the Laboureur patent are reviewed. Paragraph 5 states the Laboureur preparation has a specific activity of 8 U/mg. Paragraph 6 recounts the failed approaches using standard and modified affinity chromatography. Paragraph 7 sets forth the experimental process by which a successful pseudo-affinity approach ultimately proved successful. Contrary to the examiner's suggestion, each of these paragraphs deals with *facts*.¹ Moreover, these *facts* are more than sufficient to

¹ In fact, the declaration is almost completely devoid of conjecture, the exception being Dr. Larbre's statement that the potential advantage of higher purity UO was recognized at the time of Laboureur's work. The Office Action of November 10, 1992, however, is in agreement with Dr. Larbre. Page 4, lines 12-15.

establish that the cited references, without more, were incapable of putting applicants' high purity UO within reach of the skilled artisan.

With respect to data, applicants submit that results of failed experiments are not needed to validate Dr. Larbre's declaration. If the examiner's objection refers, instead, to the determination of the activity of Laboureur's UO preparation, applicants direct the examiner to paragraph 9 of the declaration. There, Dr. Larbre swears under penalty of law that all her statements are true or believed true. To deny weight to Dr. Larbre's declaration in the absence of a table or graph is tantamount to ignoring the oath under 18 USC §1001. Such an approach cannot be sanctioned by the MPEP or any other authority to which the examiner might point.

E. Technical Issues

In the last Office Action, the examiner makes several technical arguments to counter points made by applicants in the response filed on May 10, 1993. In order for the examiner to defend the alleged *prima facie* case, he must prevail with respect to *each* of these arguments. For the reasons provided below, however, each argument *fails* in light of factual error or legal misapplication and, therefore, the rejection is improper.

Purity of the Prior Art UO. The examiner states that "Applicants' discussion that Laboureur's urate oxidase (UO) is not pure enough to get sequences is not convincing. It is pointed out that Laboureur got pure enough UO to get [an] amino acid composition and that even a band of UO on a gel is sufficient protein to get [an] amino acid sequence." Applicants could not disagree more strenuously. First, just because amino acid *composition* data is provided, that does not mean that amino acid *sequence* data could be determined. In fact, *any* protein

preparation, regardless of how heterogeneous, will yield amino acid *composition* data. Thus, the examiner's reliance upon the presence of the amino acid composition data is completely misplaced.

Second, the examiner's off-hand comment regarding sequencing of gel purified protein is a gross oversimplification of the complicated area of protein purification. Certainly, the examiner does not suggest that this bare statement enables the sequencing of every protein. In the absence of some *evidence* that Laboureur obtained UO of sequenceable grade, by gel purification or some other method, the examiner has not established that the prior art suggested even the possibility of (i) *obtaining* a UO sequence, (ii) *designing* of a UO-specific nucleic acid probe or (iii) *cloning* of the UO gene.

Despite the legal impropriety of so doing, applicants believe that the examiner would place the burden of proving that Laboureur's UO *entirely* on applicants. Thus, applicants have endeavored to forestall such an argument by providing data which proves *conclusively* that Laboureur's UO contained significant levels of contamination. The table provided below shows a comparison of the amino acid composition given for the UO preparation in Laboureur's patent and the amino acid composition of applicants' deduced UO sequence.

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AMINO ACIDS	URATE OXIDASE (Laboureur et al.)	URATE OXIDASE (claimed here)
Ala	3.39	6.31
Cys	0.76	1.00
Asn	11.42	5.65
Glu	12.00	6.64
Phe	3.39	3.33
Gly	2.34	4.98
His	4.11	3.65
Ile	5.05	5.98
Lys	8.55	8.30
Leu	6.52	6.64
Met	4.11	8.30
Asn	-	3.65
Pro	8.55	2.99
Gln	-	3.99
Arg	6.52	3.99
Ser	5.84	7.31
Acetyl-serine	-	3.33
Thr	6.60	8.64
Val	6.52	6.64
Trp	-	2.32
Tyr	4.35	3.30

This comparison shows that the UO prepared by Laboureur has an amino acid profile distinct from that of the UO gene cloned by applicants. These data support applicants' contention that Laboureur's UO was highly contaminated, i.e., not of sequenceable grade and, therefore, the premise for the entire rejection is discredited. For this reason alone, the rejection must fall.

Method of Reedy. The examiner also states that "It is not clear why the method of Reedy et al. would not work with *A. flavus*, but Applicants are reminded that the reference include[s] reasonable inferences and routine experimentation if Applicants are referring to trivial deficiencies." Applicants are puzzled by the examiner's confusion given that their last response stated specifically that "the RNA extraction techniques used by Reedy, while suitably applied to rat liver cells, will not work with mycelium recovered from culture of *A. flavus*."

The examiner has not challenged this statement nor has the examiner requested proof in the form of data or a declaration.² Applicants submit that, whatever the nature of the "reasonable inferences and routine experimentation" to which the examiner refers, the inapplicability of Reedy to *A. flavus* material cannot be deemed "trivial." Again, if requested, applicants would willingly detail this point in a declaration. In the absence of such a request, applicants submit that it is the examiner's burden to provide some *reason* that applicants' statement cannot be taken at face value. Because the examiner has not done this, the rejection is improper.

² Applicants point out that they offered to provide a declaration on this point if the examiner deemed such proof critical. No such request has been made.

F. Secondary Considerations

At page 4 of the last Office Action, the examiner states that "Applicants' argument that 'as no one has done this in seventeen years it is not obvious' is not understood. Do Applicants mean that 35 U.S.C. §103 rejections are improper?"³ Of course, applicants do not deny the propriety of all rejections under §103, only the propriety of the particular rejection advanced by the examiner in the instant prosecution.

In the landmark patent case *Graham v. John Deere Co.*, 148 USPQ 459 (1966), the Supreme Court validated the relevance of so-called "secondary considerations" in the determination of nonobviousness, including both "long-felt but unsolved needs" and "failure of others." In view of the examiner's statement that a more pure form of UO "would have been motivated by the desire to produce an enzyme with potentially fewer harmful contaminants, and the knowledge that urate oxidase has medical uses as is well known to one of ordinary skill in the art," applicants submit that long-felt need is beyond challenge. Moreover, the absence of any meaningful progress between the issue date of Laboureur's patent and the filing of the instant application is *prima facie* evidence that the admitted long-felt need went unsolved. Any suggestion that the absence of progress was due to lack of interest or appreciation of an invention's potential marketability, as discussed in *Scully Signal Co. v.*

³ This is a rather crude paraphrase of applicants' actual submission:

. . . [T]he failure of anyone to purify UO beyond the 8 U/mg reported by Laboureur in the seventeen years from the issuance of the Laboureur patent and the filing of the present application [refutes the examiner's allegation of obviousness].

Response filed May 10, 1993, at page 6 (emphasis in original).

Electronic Corp. of America, 196 USPQ 657 (1st Cir. 1977), would be in direct conflict with the examiner's position of record.

Applicants are aware that evidentiary submissions are often made to support long-felt but unsolved need. MPEP §716(4). In this case, where the examiner has admitted that such a long-felt need allegedly provided the motivation for applicants' invention, applicants feel that no evidentiary submission is needed. Should the examiner require evidence in the form of a declaration, applicants would gladly oblige.

G. "Obvious to Try"

If it is assumed *arguendo* that (i) the examiner's treatment of the Larbre declaration was proper, (ii) that the examiner has not made erroneous technical arguments *and* (iii) that the examiner properly declined to entertain applicants' position with respect to secondary considerations, the rejection still would be improper as relying on a flawed legal standard. As applicants suggested previously, the rejection sounds in terms of "obvious to try." The examiner has taken exception to this line of reasoning, stating that he could "not locate the sentence where he said it is obvious to try."

Despite the examiner's contention, it remains apparent that the standard being applied *is*, in fact, "obvious to try." For example, only a few lines above the examiner's disclaimer of the obvious-to-try standard, the last Office Action posits that "[the] Examiner has repeatedly stated that high purity UO is obvious." This statement is a paradigm for an obvious-to-try approach. Where is the suggestion, taken from the prior art, that one could *double* the enzyme activity of Laboureur's UO by *any* method, much less those in the articles cited by the examiner? There is no such suggestion and, therefore, the best that can be said is that the art invited those of skill to *try*

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to make higher purity UO. As the examiner has already admitted, this is an insufficient ground upon which to base a §103 rejection.

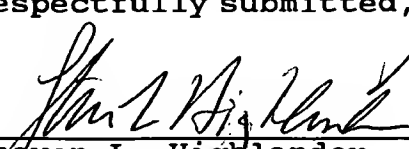
The examiner also chastises applicants for their allegedly incorrect statement of the examiner's burden. According to the examiner, because the claims are directed to a composition, the method by which the composition is made is irrelevant to the rejection. Applicants remind the examiner that references must be *enabling*. If the references do not enable a UO of at least 16 U/mg, then the references do not meet limitations of the claimed invention. Therefore, an examination of the methods by which applicants achieved a high purity UO preparation indeed are relevant to the rejection. Moreover, because the references, either alone or in combination, fail to enable applicants' claimed UO, the rejection is without merit.

CONCLUSION

In light of the foregoing amendments and remarks, applicants submit that claims 1-7 and 27-29 are in condition for allowance and solicit an early indication to that effect. Should Examiner Schmickel believe that further discussion will advance the instant prosecution, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Date


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